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Revving up cGAS

By Chris Cain, Senior Writer

Cytosolic DNA is a well-known trigger of innate immunity, but it was only last year that its primary sensor, cyclic GMP-AMP synthase, was identified.¹ Now, the first *in vivo* functional study of the protein has confirmed its essential role in antiviral immunity and strengthened the case for developing modulators of cyclic GMP-AMP signaling, including agonists that serve as adjuvants or inhibitors for autoimmune conditions.²

A core component of the innate immune response is its ability to detect and react to foreign molecules, including DNA or RNA, during viral or bacterial infections. The toll-like receptors (TLRs), which are localized to the cell surface and in endosomes, are the best-understood system for this recognition. For example, foreign DNA is detected by TLR9, which recognizes unmethylated CpG sites commonly found in bacterial and viral DNA.

At least 25 companies are developing agonists or antagonists of TLRs for a variety of indications, and 9 companies are developing products that act upon TLR9.

Recently it has become clear that TLR9-independent pathways of DNA sensing also exist. For example, transmembrane protein 173 (STING; TMEM173), an endoplasmic reticulum protein, was shown to be required for intracellular DNA-mediated, TLR9-independent immunity. Mice lacking Sting are particularly susceptible to viral and bacterial infection and have an impaired type I interferon (IFN) response.

Although there was widespread agreement that STING is a required component of the immune response to intracellular DNA, it remained hotly debated how intracellular DNA was being recognized by cells.

One hypothesis is that STING is a direct DNA sensor,³ along with a handful of other proteins. Separately, studies have shown that STING recognizes another substrate, cyclic-di-GMP, a secondary signaling molecule widely produced and used by bacteria.⁴

Last December, a team from **The University of Texas Southwestern Medical Center** filled in the missing piece of the puzzle with the discovery of cyclic GMP-AMP synthase (cGAS). The group, led by **Howard Hughes Medical Institute** investigator and UT Southwestern

“STING has been implicated in certain autoimmune diseases, and I’m pretty sure they would also be cGAS dependent, so it would be quite interesting to design analogs of cGAMP that inhibit STING or to inhibit cGAS itself.”

— Veit Hornung,
University of Bonn

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Medical Center professor of molecular biology Zhijian Chen, biochemically mapped out a pathway in which cGAS directly binds and is activated by cytosolic DNA, which leads to the production of a previously unknown signaling molecule, cyclic GMP-AMP (cGAMP).

cGAMP then binds and activates STING, triggering a signaling cascade that leads to the production of IFN (see Figure 1, “Cyclic GMP-AMP signaling in the immune response”).^{1,5}

Veit Hornung, professor of clinical biochemistry at the University of Bonn, told SciBX that the study was a breakthrough. “How DNA is sensed in the cytosol was one of the last big questions left in the field of pattern recognition. The field had been very complicated prior to the discovery of cGAS,” he said. “Now it has become clear that this is the primary route for cytosolic DNA sensing.”

Over the last 10 months, a host of labs including Hornung’s have characterized the pathway in additional detail, solving crystal structures of both cGAS in complex with DNA and STING in complex with cGAMP.⁶⁻¹⁰

Now, Chen’s group has provided the best evidence to date to support the functional importance of this signaling pathway in antiviral immunity.

In one series of experiments, his group sought to determine whether cGAS mediates an immune response to retroviral infection.¹¹ In cells lacking cGAS, infection with HIV, simian immunodeficiency virus (SIV) or murine leukemia virus (MLV) triggered no IFN response, whereas infection with a control RNA virus led to a strong IFN response.

In cultured human cells that express cGAS, infection with HIV induced the production of cGAMP as measured by mass spectrometry.

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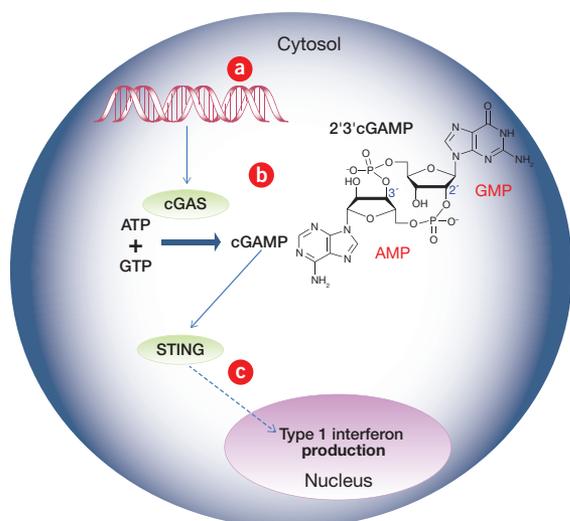


Figure 1. Cyclic GMP-AMP signaling in the immune response.

Although cytosolic DNA (a) has long been known to trigger an immune response, it was only this year that its primary molecular sensor was identified. The sensor, cyclic GMP-AMP synthase (cGAS), is activated by binding directly to DNA, and it subsequently synthesizes cyclic GMP-AMP (cGAMP) from ATP and GTP (b). cGAMP is a soluble molecule that can be transmitted from cell to cell between tight junctions. It directly binds to transmembrane protein 173 (STING; TMEM173), triggering a signaling cascade that leads to the production of type I interferon (c).

There are two therapeutic options for manipulating the pathway. To stimulate an immune response against a foreign infection, cGAMP could be given as an adjuvant that induces a type I interferon response. To prevent inflammation, which can be caused by host DNA entering the cytoplasm, inhibitors of cGAMP could be developed.

In a second series of experiments, Chen's team generated *cGas* knockout mice and characterized their response to DNA transfection and DNA-virus infection *in vitro* and *in vivo*.² In fibroblasts, macrophages and dendritic cells, *cGas* knockout eliminated the production of IFN in response to purified DNA or infection with herpes simplex virus (HSV), whereas wild-type cells generated expected levels of IFN.

In *cGas* knockout mice, HSV infection generated significantly less IFN response and decreased survival compared with infected mice that had intact *cGas*.

Finally, the group showed that cGAMP can act as a vaccine adjuvant. In mice, the model antigen ovalbumin plus cGAMP induced an IFN response and increased antibody production and antigen-specific CD8⁺ T cell responses compared with ovalbumin alone.

Results were published in two separate *Science* articles.

cGAMP ramp

Chen said that the results provide the first evidence that cGAMP could act as an adjuvant but noted that it is still far from clear how the molecule would stack up against other approaches.

"This approach mimics the stimulatory effect of DNA, which is

mediated by cGAS, so by using this molecule you can more directly trigger an immune response," he said. "It's a bit premature to say how this will compare with other adjuvants; studies would have to be done side by side, and in the context of viral infections."

Chen and Christophe Desmet, a research fellow in cellular and molecular immunology at the **University of Liege**, said that one potential advantage could be cGAMP's ability to induce a robust CD8⁺ T cell response, which is characteristic of DNA-based vaccines.

Multiple DNA-based influenza and HIV vaccines are in development with the goal of increasing efficacy by generating a robust CD8⁺ T cell response.

However, Desmet cautioned, "DNA vaccines generally don't work well in humans. They work fine in mice but then they are not strongly immunogenic in humans, and we still don't know why that is."

Last year, Desmet led a team that showed that the commonly used adjuvant alum induces an immune response in part by triggering DNA release from host cells.¹² He thus wants to see studies exploring whether cGAS could be contributing to alum's function.

Hornung said that it makes sense to test how cGAMP behaves as an adjuvant given the evidence that it is a key DNA-sensing pathway. He did say that there is little industry appetite for developing new adjuvants for prophylactic vaccines given the extremely high safety bar.

In February, the FDA issued a complete response letter for **Dynavax Technologies Corp.**'s Heplisav HBV vaccine, which is formulated with an immunostimulatory DNA adjuvant that agonizes TLR9.¹³

"cGAMP is a very potent interferon producer, and some companies may not like that idea, though this may be more emotional than rational," Hornung said.

Doing the opposite

Hornung argued that a more promising therapeutic tack may be to develop and test inhibitors of cGAS in autoimmune indications.

"STING has been implicated in certain autoimmune diseases, and I'm pretty sure they would also be cGAS dependent, so it would be quite interesting to design analogs of cGAMP that inhibit STING or to inhibit cGAS itself," he said. He added that multiple labs, including his own, are pursuing the strategy.

Chen said that his lab also is pursuing the target. "cGAS is quite amenable to small molecule inhibition and could be a very attractive target for treating autoimmune diseases," he said.

Last year, researchers at the **University of Miami Miller School of Medicine** showed that knocking out *STING* could prevent DNA-induced inflammatory disease in a mouse model.¹⁴

Ken Ishii, project leader at the Laboratory of Adjuvant Innovation at the **National Institute of Biomedical Innovation** and adjunct professor of vaccine science at **Osaka University**, agreed that blocking the pathway may be a more attractive avenue than adjuvant design.

"cGAS, as an enzyme critical in the DNA-STING-interferon-autoimmunity pathway, should be one of the best candidates to target for developing therapeutic approaches for many autoimmune diseases, including SLE [systemic lupus erythematosus]," he said.

He added that the possible role of cGAS in autoimmune diseases raises safety concerns about using cGAMP at high concentrations as an adjuvant.

Chen said that thus far, "*cGas* knockout phenotypes are virtually

identical to the *Sting* knockout.” He did say there could be differences uncovered as the model is characterized in more detail.

Hornung and Desmet agreed that the knockout mouse will likely be rapidly tested in models of bacterial and viral infection and autoimmune disease.

Hornung is continuing to study the effect of cGAMP *in vivo*. Last month in work published in *Nature*, his lab showed that cGAMP can spread from cell to cell to propagate an immune response.¹⁵

The pace of research on cGAMP continues to heat up. Last week, University of Miami Miller School of Medicine researchers published in *Cell* that even as cGAMP activates STING directly, it can also act on a separate AMP-activated protein kinase (AMPK) pathway to suppress sustained STING activation.¹⁶

This suggests that cGAMP can both trigger and put the brakes on an immune response and reinforces the fact that cGAMP’s functions are not fully fleshed out.

Chen’s group has filed patent applications covering the use of cGAMP as an adjuvant and targeting cGAS to treat autoimmune diseases. Their licensing status was not disclosed.

Cain, C. *SciBX* 6(40); doi:10.1038/scibx.2013.1117
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REFERENCES

1. Sun, L. *et al. Science* **339**, 786–791 (2013)
2. Li, X.-D. *et al. Science*; published online Aug. 29, 2013; doi:10.1126/science.1244040
Contact: Zhijian J. Chen, The University of Texas Southwestern Medical Center, Dallas, Texas
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3. Abe, T. *et al. Mol. Cell* **50**, 5–15 (2013)
4. Burdette, D.L. *et al. Nature* **478**, 515–518 (2011)
5. Wu, J. *et al. Science* **339**, 826–830 (2013)
6. Gao, P. *et al. Cell* **153**, 1094–1107 (2013)
7. Ablasser, A. *et al. Nature* **498**, 380–384 (2013)
8. Civril, F. *et al. Nature* **498**, 332–337 (2013)
9. Kranzusch, P.J. *et al. Cell Rep.* **3**, 1362–1368 (2013)
10. Zhang, X. *et al. Mol. Cell.* **51**, 226–235 (2013)
11. Gao, D. *et al. Science*; published online Aug. 8, 2013; doi:10.1126/science.1240933
Contact: Zhijian J. Chen, The University of Texas Southwestern Medical Center, Dallas, Texas
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12. Marichal, T. *et al. Nat. Med.* **17**, 996–1002 (2011)
13. Haas, M. *BioCentury* **21**(9), A8; March 4th, 2013
14. Ahn, J. *et al. Proc. Natl. Acad. Sci. USA* **109**, 19386–19391 (2012)
15. Ablasser, A. *et al. Nature*; published online Sept. 29, 2013; doi:10.1038/nature12640
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16. Konno, H. *et al. Cell*; published online Oct. 8, 2013; doi:10.1016/j.cell.2013.09.049
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COMPANIES AND INSTITUTIONS MENTIONED

- Dynavax Technologies Corp.** (NASDAQ:DVAX), Berkeley, Calif.
- Howard Hughes Medical Institute**, Chevy Chase, Md.
- National Institute of Biomedical Innovation**, Osaka, Japan
- Osaka University**, Osaka, Japan
- University of Bonn**, Bonn, Germany
- University of Liege**, Liege, Belgium
- University of Miami Miller School of Medicine**, Miami, Fla.
- The University of Texas Southwestern Medical Center**, Dallas, Texas

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Clinical takeoff for new epigenetic targets

By Kai-Jye Lou, Senior Writer

There is little doubt that 2014 will be a banner year for next-generation epigenetics companies, with key clinical data expected for next-generation drugs and first-generation candidates that target new epigenetic regulators. But the big biotech and pharma companies that carved up the space in recent years might have clinical data even sooner, as the **American Society of Hematology** meeting in December should provide a window into at least two candidates in hematologic malignancies.

Clinical data aside, the epigenetics space itself continues to expand and mature, with multiple companies being founded, one going public and larger companies continuing to place bets in the field through

partnerships, acquisitions and option deals (*see* Table 1, “Selected recent deals and partnerships in the epigenetics space”).

The landscape in epigenetics can be divided into two major segments. One includes companies developing compounds against epigenetic regulators not already targeted by marketed drugs. The other includes companies developing second-generation compounds against validated epigenetic drug targets (*see* Table 2, “Selected clinical stage compounds that target epigenetic regulators”).

New compounds for new targets

Researchers started linking new classes of epigenetic regulators to the pathology of many human diseases over a decade ago, particularly in genetically defined subsets of cancers.

These include histone methyltransferases (HMTs), proteins in the BET bromodomain family and lysine demethylases. Specific examples include bromodomain containing 4 (BRD4), lysine-specific histone demethylase 1 (KDM1A; LSD1) and a trio of HMTs: DOT1L, enhancer of zeste homolog 2 (EZH2) and nuclear SET domain-containing protein 2 (WHSC1; MMSET; NSD2).

NSD2 was the first of these epigenetic regulators to be associated

Table 1. Selected recent deals and partnerships in the epigenetics space. The January 2012 deal between the **Genentech Inc.** unit of **Roche** and **Constellation Pharmaceuticals Inc.** set off a new wave of dealmaking activity in the epigenetics space. **Celgene Corp.** made a \$15 million equity investment in **Acetylon Pharmaceuticals Inc.** that gave the biopharma an observational seat on Acetylon’s board and followed up with the **Epizyme Inc.** partnership that included a \$90 million up-front payment and equity investment in the now-public company. Celgene then announced in July that it paid \$100 million up front in exchange for an exclusive option to acquire the company. Other notable deals include **GlaxoSmithKline plc** taking out Cellzome AG and **Rodin Therapeutics Inc.’s** partnership with **Proteros biostructures GmbH** and **Johnson & Johnson** to develop new therapies for CNS diseases.

Source: *BioCentury Archives*

| Company/institution | Deal focus | Financial terms | Date |
|--|---|---|---------------|
| Constellation Pharmaceuticals; Genentech | Three-year partnership to use Constellation’s platform to discover and develop small molecules against undisclosed epigenetic targets for cancer and other diseases; excludes rights to BET family of bromodomain-containing proteins and enhancer of zeste homolog 2 (EZH2) | Constellation receives \$95 million up front plus research funding and is eligible for undisclosed milestones and royalties; Genentech has option to acquire Constellation | January 2012 |
| Acetylon Pharmaceuticals; Celgene (NASDAQ:CELG) | Celgene takes equity stake in selective histone deacetylase inhibitor developer Acetylon; gets an observational, nonvoting board seat at Acetylon but does not receive rights or options to any technology | Celgene makes \$15 million equity investment in Acetylon | February 2012 |
| Celgene; Epizyme (NASDAQ:EPZM) | Partnership to discover, develop and commercialize cancer therapeutics that inhibit histone methyltransferases; Celgene gets ex-U.S. rights to B7 and has an exclusive, three-year option to license ex-U.S. rights for unpartnered histone methyltransferase inhibitors, with a potential one-year extension | Epizyme receives \$90 million up front, which includes an undisclosed minority equity investment; Epizyme is eligible for more than \$160 million in milestones for each licensed program, plus double-digit royalties on ex-U.S. sales | April 2012 |
| Cellzome AG; GlaxoSmithKline (LSE:GSK; NYSE:GSK) | GSK acquires Cellzome; companies had partnered in 2010 to discover small molecules against epigenetic targets | GSK acquires the 80.02% of Cellzome it does not already own for £61 million (\$98 million) in cash | May 2012 |
| Oncoethix S.A.; Mitsubishi Tanabe Pharma Corp. (Tokyo:4508; Osaka:4508) | Oncoethix gets exclusive, worldwide rights to BET bromodomain inhibitor OTX015 and will develop the compound to treat leukemia and other hematologic malignancies; Mitsubishi retains rights to OTX015 in certain Asian countries | Undisclosed | June 2012 |
| Life Technologies Corp. (NASDAQ:LIFE); ^A Structural Genomics Consortium; The University of Chicago; University of Toronto | Partnership to develop and commercialize recombinant antibodies against epigenetic targets | Undisclosed | July 2012 |

(Continues on p. 6)

Table 1. Selected recent deals and partnerships in the epigenetics space. (continued)

| Company/institution | Deal focus | Financial terms | Date |
|---|--|---|----------------|
| Astex Pharmaceuticals Inc., ^B Cancer Research UK; The Institute of Cancer Research | Partnership to discover and develop oral therapies against an undisclosed epigenetic target in a blood cancer | Astex and Institute of Cancer Research share undisclosed funding from Cancer Research UK | September 2012 |
| Constellation; Leukemia & Lymphoma Society | LLS to provide funding to support development of Constellation's small molecule BET inhibitors to treat hematologic malignancies through Phase I testing | LLS will provide up to \$7.5 million | September 2012 |
| Evotec AG (Xetra:EVT); Dana-Farber Cancer Institute | Partnership to discover and commercialize cancer treatments that target epigenetic drug mechanisms; partners will validate epigenetic targets and demonstrate the druggability of selected target families | Undisclosed | May 2013 |
| Proteros biostructures; Rodin Therapeutics; Johnson & Johnson (NYSE:JNJ) | Neurology epigenetics startup Rodin partners with Proteros, J&J's Janssen Research & Development LLC unit and the pharma's Boston Innovation Center ; Proteros gives Rodin access to its structural biology platform and will help with early drug discovery work around screening, profiling and early chemical optimization | Rodin has undisclosed financing from Atlas Venture and Johnson & Johnson Development Corp. ; Proteros gets an equity stake in Rodin | June 2013 |
| Acetylon; Celgene | Celgene gets exclusive option to acquire Acetylon | Acetylon receives \$100 million up front; if Celgene exercises the option, Acetylon will receive at least \$500 million up front and Acetylon shareholders would be eligible for up to \$250 million in regulatory milestones and up to \$850 million in sales milestones | July 2013 |
| Astex; Otsuka Pharmaceutical Co. Ltd. | Otsuka acquires Astex | Otsuka acquired Astex for \$8.50 per share, or about \$866 million in cash | September 2013 |

^ABeing acquired by **Thermo Fisher Scientific Inc.** (NYSE:TMO). ^BAcquired by Otsuka Pharmaceutical.

with cancer, as separate groups from the Netherlands and **Weill Cornell Medical College** in 1998 linked it to the pathogenesis of multiple myeloma (MM).^{1,2}

Researchers took notice of EZH2 in 2000 after multiple European groups linked it to the pathogenesis of leukemia and lymphoma.^{3,4} BRD4 appeared on the radar a year later after a group at **Brigham and Women's Hospital** linked rearrangements in its gene to aggressive carcinomas.⁵

In 2005, a group at **The University of North Carolina at Chapel Hill** linked DOT1L to leukemogenesis in humans,⁶ and a separate group in Germany suggested that targeting LSD1 could be a new way to regulate androgen receptor function and proliferation in tumor cells.⁷

Despite the disease associations, it was unclear whether the epigenetic regulators were druggable. Recently, researchers in academia and at companies began publishing compounds as well as structural and biological data to suggest these proteins are, indeed, druggable.⁸

Constellation Pharmaceuticals Inc., Epizyme Inc. and **GlaxoSmithKline plc** have been at the forefront of R&D activity against these newer classes of epigenetic regulators.

Epizyme has partnerships with GSK, **Eisai Co. Ltd.** and **Celgene Corp.**, which were announced in January and March of 2011 and April 2012, respectively.⁹ Constellation signed an R&D partnership with the **Genentech Inc.** unit of **Roche** last January.¹⁰

In September 2012, Epizyme started a Phase I trial of its DOT1L inhibitor, EPZ-5676, in leukemia with rearrangements in the *myeloid-lymphoid or mixed-lineage leukemia (MLL; HRX)* gene. The company said that it plans to report top-line data and expand the Phase I trial this quarter. The compound is partnered with Celgene.

This past June, Epizyme began a Phase I/II trial of its selective EZH2 inhibitor, EPZ-6438, to treat patients with non-Hodgkin's lymphoma (NHL) who have a mutation in the gene. The company said that it plans to report top-line data and start Phase II testing next year. The compound is partnered with Eisai.

"These two compounds represent the first HMT inhibitors to transition into the clinic, and they will provide the first tests of the concept of treating genetically defined cancers with potent and selective HMT inhibitors in patient populations that are defined by genetic lesions affecting specific HMTs," said Robert Copeland, EVP and CSO at Epizyme.

No compounds have been disclosed under the Epizyme-GSK partnership, which covers small molecules that target undisclosed HMTs, excluding DOT1L and EZH2.

Public investors were quick to reward Epizyme for its clinical and partnering progress. In May, the company raised \$88.7 million in an IPO that valued it at \$426.2 million. Shares in the company rose from the \$15 IPO price to \$22.99 after the first day of trading. Epizyme closed at \$35.85 on Oct. 11, with a valuation just north of \$1 billion.

GSK started a Phase I trial of its bromodomain inhibitor, GSK525762, in March 2012. Data are expected in late 2014 or early 2015. The pharma is evaluating the inhibitor in patients who have nuclear protein in testis (C15orf55; NUT) midline carcinoma and other cancers.

Data from more recent studies also suggest that the bromodomain inhibitor could have therapeutic utility in nononcology indications.

In 2010, a group led by researchers at GSK and **The Rockefeller University** showed that GSK525762 had potent, broad-spectrum

Table 2. Selected clinical stage compounds that target epigenetic regulators. The availability of new research tools and data on epigenetic regulators has driven the development of a new wave of compounds. Many of these compounds recently entered Phase I trials, and companies now point to Phase II data as the next milestone that will be key to determining which molecules and their respective targets will pan out for the field. Table excludes class-selective and pan-histone deacetylase (HDAC) inhibitors.

Source: *BCIQ: BioCentury Online Intelligence; BioCentury Archives*

| Company | Compound | Description | Indication | Status | Milestone(s) |
|---|----------------------|--|--|--|---|
| Acetylon Pharmaceuticals Inc. | ACY-1215 | Oral selective HDAC6 inhibitor | Multiple myeloma (MM) | Phase Ib | Start Phase II (early 2014); additional Phase Ib data (December 2013) |
| Astex Pharmaceuticals Inc. ^A | SGI-110 | Small molecule DNA methyltransferase inhibitor | Liver cancer; acute myelogenous leukemia (AML); myelodysplastic syndrome (MDS); ovarian cancer | Phase II; Phase I/II; Phase I/II; Phase I/II | Phase II data (December 2013) |
| Constellation Pharmaceuticals Inc. | CPI-0610 | BET bromodomain inhibitor | Lymphoma | Phase I | Undisclosed |
| Epizyme Inc. (NASDAQ:EPZM); Eisai Co. Ltd. (Tokyo:4523; Osaka:4523) | EPZ-6438 | Selective inhibitor of enhancer of zeste homolog 2 (EZH2) | Non-Hodgkin's lymphoma (NHL) | Phase I/II | Phase I data (2014); start Phase II (2014) |
| Epizyme; Celgene Corp. (NASDAQ:CELG) | EPZ-5676 | Histone methyltransferase DOT1L (DOT1L) inhibitor | Leukemia | Phase I | Phase I data (4Q13) |
| GlaxoSmithKline plc (LSE:GSK; NYSE:GSK) | GSK525762 | Bromodomain inhibitor | Epithelial cancer | Phase I | Phase I data (YE14 or early 2015) |
| Oncoethix S.A.; Mitsubishi Tanabe Pharma Corp. (Tokyo:4508; Osaka:4508) | OTX015 | Synthetic small molecule inhibitor of BET bromodomain containing 2 (BRD2), BRD3 and BRD4 | Hematologic malignancies | Phase I | Unavailable |
| Resverlogix Corp. (TSX:RVX) | RVX-208 ^B | Inhibitor of the BET family of bromodomain-containing proteins, including BRD4 | Atherosclerosis | Phase IIb | Unavailable |

^AAcquired by **Otsuka Pharmaceutical Co. Ltd.** ^BCompany had reported top-line Phase II data from the 324-patient trial showing that RVX-208 missed the primary endpoint of 0.6% reduction in atheroma volume from baseline at 26 weeks, but subsequent analysis identified a 92-patient subgroup with 1.4% reduction in atheroma volume from baseline at 26 weeks.

anti-inflammatory properties.¹¹ A separate group led by researchers at the **La Jolla Institute for Allergy & Immunology** showed in 2012 that the compound also could inhibit autoimmunity.¹² Researchers from GSK's immuno-inflammatory disease-focused EpiNova Epigenetics discovery performance unit (DPU) collaborated on both studies.

The pharma has at least one more DPU dedicated to the epigenetics space—the Cancer Epigenetics DPU.

GSK also is one of several pharmas partnered with the **Structural Genomics Consortium**, a not-for-profit organization that leads a precompetitive consortium focused on the development of open-access chemical probes to modulate epigenetic proteins.

In September, Constellation started a Phase I trial of the BET protein bromodomain inhibitor CPI-0610 in patients with previously treated and progressive lymphomas. The biotech also has inhibitors of EZH2 in preclinical development for cancer.

Constellation declined to disclose when it expects to report data or start Phase II trials of CPI-0610.

For this segment of the epigenetics space, Simon Jones thinks the key milestones are going to be Phase II efficacy data. Jones is VP of biology and preclinical development at **Acetylon Pharmaceuticals Inc.**, which is developing isoform-selective histone deacetylase (HDAC) inhibitors.

"I think everyone in this space is eagerly awaiting the efficacy data that will come from the future Phase II trials evaluating these compounds," Jones told *SciBX*. He noted that such data will be critical

for determining which epigenetic regulators to target in new R&D programs and will help drive further deal activity.

"If positive results are observed, these may trigger additional interest within the investment community, perhaps leading to additional public offerings by various companies in the epigenetic space and potentially some movement in M&A activities," Copeland added.

Attention to the old

Companies working in the other segment of the epigenetics space are focused on developing compounds that have better safety and efficacy than first-generation drugs that inhibit HDACs or DNA methyltransferases. The hope is that these second-generation compounds will be more amenable for use in combination therapy and have applicability to a broader range of diseases, including those outside the oncology space.

Companies in this space include Astex Therapeutics Inc. and Acetylon.

On Oct. 11, **Otsuka Pharmaceutical Co. Ltd.** completed its acquisition of Astex for about \$866 million in cash. Astex markets Dacogen decitabine, a first-generation hypomethylating agent that inhibits DNA methyltransferase, to treat myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML).

Astex's next-generation version of Dacogen, a dinucleotide prodrug called SGI-110, is in a Phase II trial to treat hepatocellular carcinoma (HCC), a Phase I/II trial to treat MDS and AML and a Phase I/II trial to

treat ovarian cancer. The hope is that SGI-110 will have greater stability, less toxicity and require less frequent dosing than Dacogen.

The company reported top-line Phase II data for the AML and MDS trial this August that showed an overall remission rate of 25% in the 67 evaluable patients with AML who had a minimum follow-up of three months. Astex said that it will present detailed results from the trial at the American Society of Hematology meeting in December.

Whereas Otsuka has taken the acquisition route, Celgene's approach has been strategic investments and option deals.

Celgene made a \$15 million equity investment in Acetylon in February 2012 and received an observational seat on the company's board. This year, Celgene made a \$100 million up-front payment to Acetylon for an exclusive option to acquire the company.

The payment eclipses the \$95 million up-front payment that Genentech made to Constellation, making it the largest disclosed initial dollar outlay in the epigenetics space.

Celgene's partnership with Epizyme includes a \$90 million up-front payment, which also gave it an undisclosed minority equity stake.

Acetylon's ACY-1215, an oral, selective HDAC6 inhibitor, is in Phase Ib testing to treat patients with relapsed or refractory MM. The company is evaluating ACY-1215 in combination with either the immunomodulatory agent Revlimid lenalidomide or the proteasome inhibitor Velcade bortezomib.

The company reported interim Phase Ib data for ACY-1215 in June and plans to report additional data at the American Society of Hematology meeting. Jones said that Acetylon is aiming to start Phase II trials early next year.

In 2005, researchers at **Harvard Medical School** and the **Broad Institute of MIT and Harvard** published data from studies in clinical samples suggesting that inhibition of HDAC6 could have synergistic antitumor effects with Velcade in MM.¹³

Celgene markets Revlimid to treat MM, MDS and mantle cell lymphoma (MCL). **Takeda Pharmaceutical Co. Ltd.'s Millennium Pharmaceuticals Inc.** unit markets Velcade in the U.S. to treat MM and MCL. **Johnson & Johnson** has ex-U.S. rights.

Jones cited two factors that have driven the field's shift toward the development of selective HDAC inhibitors: the known toxicity of pan-HDAC inhibitors, which renders them challenging for use in combination with other cancer drugs, and a deeper understanding of the biology of individual HDACs as therapeutics targets.

The two approved pan-HDAC inhibitors are Celgene's Istodax romidepsin and **Merck & Co. Inc.'s** Zolinza vorinostat. Both are marketed to treat cutaneous T cell lymphoma (CTCL). Istodax also is marketed to treat peripheral T cell lymphoma (PTCL).

Another notable event in this segment of the epigenetics space is **Syndax Pharmaceuticals Inc.'s** closing of a \$26.6 million series B round in August. The biotech's lead compound is entinostat, an inhibitor selective for class I HDACs that is in multiple Phase II trials to treat various hematologic malignancies and solid tumors.

Compounds that inhibit HDAC1, HDAC2 and HDAC3—all class I

HDACs—generally have strong antiproliferative and apoptosis-inducing activity.¹⁴ Dysregulation of HDAC1 and HDAC2 also has been implicated in multiple neurodegenerative conditions.¹⁵

"A further breakthrough for the new generation of selective HDAC inhibitors will be in moving them into nononcology domains in the clinic," Jones told *SciBX*.

In 2010, researchers at the Broad Institute and Harvard Medical School published data from a chemical genetics screen suggesting that combined inhibition of HDAC1 and HDAC2 could help stimulate the production of fetal hemoglobin,¹⁶ which could be useful for treating sickle cell disease and β -thalassemia.

Acetylon has selective inhibitors that target both HDAC1 and HDAC2 in preclinical development for neurodegenerative diseases, sickle cell disease and β -thalassemia.

Last December, the company showed that one of its own selective inhibitors of HDAC1 and HDAC2 could stimulate the production of fetal hemoglobin in human bone marrow cells.

Jones expects these programs to start Phase I trials by early 2015.

Recent entrants

The heightened degree of industry interest in the epigenetics space also has resulted in the formation of several new companies in recent years. These include **Rodin Therapeutics Inc.**, **Syros Pharmaceuticals Inc.**, **Tensha Therapeutics Inc.** and **Zenith Epigenetics Corp.**

Tensha was founded in July 2011 and closed a \$15 million series A round that September. The company is developing small molecule bromodomain inhibitors to treat cancer and inflammatory diseases.¹⁷

Syros was founded in 2012 and closed a \$30 million series A round this past April. The company is focused on mapping a class of regulatory DNA regions called super-enhancers to identify druggable oncogenic drivers and guide the development of small molecules that selectively inhibit cancer cell growth.¹⁸

Rodin and Zenith were both founded this year. Rodin raised an undisclosed amount in a seed round that is tied to a committed, tranced series A round. The company is developing epigenetic small molecule modulators to treat CNS disorders, including Alzheimer's disease (AD).

Zenith spun out from **Resverlogix Corp.** and is developing compounds that target the BET family of bromodomain-containing proteins for multiple diseases, including autoimmune diseases and cancer.

Lou, K.-J. *SciBX* 6(40); doi:10.1038/scibx.2013.1118
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REFERENCES

1. Stec, I. *et al. Hum. Mol. Genet.* **7**, 1071–1082 (1998)
2. Chesi, M. *et al. Blood* **92**, 3025–3034 (1998)
3. Cardoso, C. *et al. Eur. J. Hum. Genet.* **8**, 174–180 (2000)
4. Raaphorst, F.M. *et al. Am. J. Pathol.* **157**, 709–715 (2000)
5. French, C.A. *et al. Am. J. Pathol.* **159**, 1987–1992 (2001)
6. Okada, Y. *et al. Cell* **121**, 167–178 (2005)

"If positive results are observed, these may trigger additional interest within the investment community, perhaps leading to additional public offerings by various companies in the epigenetic space and potentially some movement in M&A activities."
—Robert Copeland, Epizyme Inc.

7. Metzger, E. *et al. Nature* **437**, 436–439 (2005)
8. Arrowsmith, C.H. *et al. Nat. Rev. Drug Discov.* **11**, 384–400 (2012)
9. Bouchie, A. *BioCentury* **20**(18), A5–A6; April 30, 2012
10. Bouchie, A. & Fulmer, T. *BioCentury* **20**(4), A1–A5; Jan. 23, 2012
11. Nicodeme, E. *et al. Nature* **468**, 1119–1123 (2010)
12. Bandukwala, H.S. *et al. Proc. Natl. Acad. Sci. USA* **109**, 14532–14537 (2012)
13. Hideshima, T. *et al. Proc. Natl. Acad. Sci. USA* **102**, 8567–8572 (2005)
14. Witt, O. *et al. Cancer Lett.* **277**, 8–21 (2009)
15. Chuang, D.-M. *et al. Trends Neurosci.* **32**, 591–601 (2009)
16. Bradner, J.E. *et al. Proc. Natl. Acad. Sci. USA* **107**, 12617–12622 (2010)
17. Cain, C. *BioCentury* **19**(38), A11; Sept. 12, 2011
18. Cain, C. *BioCentury* **21**(15), A12; April 15, 2012

COMPANIES AND INSTITUTIONS MENTIONED

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Constellation Pharmaceuticals Inc., Cambridge, Mass.

Eisai Co. Ltd. (Tokyo:4523; Osaka:4523), Tokyo, Japan
Epizyme Inc. (NASDAQ:EPZM), Cambridge, Mass.
Genentech Inc., South San Francisco, Calif.
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Harvard Medical School, Boston, Mass.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
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Tensha Therapeutics Inc., Cambridge, Mass.
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Weill Cornell Medical College, New York, N.Y.
Zenith Epigenetics Corp., Calgary, Alberta, Canada

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HER2's outside help

By Lev Osherovich, Senior Writer

An international team has found that neurokinin 1 substance P receptor, a known player in nausea, pain and inflammation, enhances HER2 signaling in breast cancer.¹ The findings argue for combining antagonists against both receptors to treat cancer.

HER2 (EGFR2; ErbB2; neu) is a receptor tyrosine kinase (RTK) that promotes aggressive tumor growth in about 30% of breast cancers.

Four HER2 inhibitors and anti-HER2 mAbs are marketed for breast cancer, non-small cell lung cancer (NSCLC) and gastric cancer, and at least a dozen more are in Phase II and Phase III testing for a range of solid tumors.

Efforts to target HER2 and related receptors in the epidermal growth factor receptor (EGFR) family traditionally have focused on preventing receptor dimerization and kinase activation. However, recent studies in cell culture and animals have pointed to an additional path to EGFR activation.

Cell culture studies have shown that HER2 and other EGFRs can be activated by a variety of GPCRs including protease-activated receptor 1 (PAR1),² KISS1 receptor (KISS1R; GPR54)³ and angiotensin II type 1 receptor (AGTR1).⁴

Now, a team led by Vanessa Almendro, group leader at the **Hospital Clinic of Barcelona** and visiting scientist at the **Dana-Farber Cancer Institute**, has found that

HER2 can be activated *in vivo* by another GPCR—neurokinin 1 substance P receptor (TACR1).

HER2 too

Last year, Almendro's team found that blocking substance P, the principal ligand of TACR1, reduced HER2⁺ breast cancer growth *in vitro*.⁵ In the new study, the team showed that TACR1 is responsible for substance P's effect on HER2 activity.

Almendro's team found that *TACR1* was overexpressed in 94% of 318 HER2⁻ and HER2⁺ patient-derived breast tumor samples. HER2⁺ tumors had even higher *TACR1* expression than HER2⁻ tumors.

In vitro, HER2⁺ tumor cells showed more rapid HER2 phosphorylation and activation upon treatment with substance P than untreated cells. Likewise, forced overexpression of *TACR1* increased HER2 signaling in tumor cells and small interfering RNA knockdown or pharmacological inhibition of TACR1 decreased HER2 activation compared with what was seen in wild-type controls.

Pharmacological inhibition of TACR1 reduced growth of HER2⁺ but not HER2⁻ tumors in a mouse xenograft model of breast cancer.

Almendro told *SciBX* that she suspects chronic activation of TACR1 leads to upregulation of HER2, feeding tumor growth and reducing the efficacy of HER2 inhibitors. Indeed, cultured HER2⁺ cells chronically exposed to substance P had higher levels of HER2 and lower response to three small molecule HER2 inhibitors than untreated cells.

"Substance P and other signals that activate HER2 are likely to contribute to resistance to treatment," said Almendro.

The team did not examine how TACR1 activation affected response to HER2 mAbs.

Results were reported in *Cancer Research*.

Mechanism to therapy

Almendro's finding is the most clear-cut example to date for cross-activation of EGFR family members by GPCRs in cancer. Nevertheless, mechanistic questions remain about precisely how TACR1 and other GPCRs contribute to tumor growth.

One hypothesis is that GPCRs like TACR1 have distinct functions beside their normal role of turning on downstream G proteins. Binding to EGFR-family proteins could be one such function.

"GPCRs could act apart from their G proteins to interact with EGFRs and hijack their signaling," said Walter Thomas, a professor and chair of general physiology and head of the School of Biomedical Sciences at **The University of Queensland**.

Thomas noted that although previous cell culture studies have implicated other GPCRs in tumor growth, it has been difficult to draw a clear connection between specific EGFR-family proteins and GPCRs because of the complex downstream effects of modulating GPCR pathways.

"It's pretty definitive that knocking down *TACR1* causes loss of growth-promoting signaling by substance P," said Thomas. "This is good evidence of a direct link between HER2 and TACR1."

Last month, Thomas' team reported a genetic screen that identified a slew of downstream signaling components involved in the activation of EGFR signaling by AGTR1.⁶

Almendro favors the idea that TACR1 recruits other kinases to the plasma membrane, leading to phosphorylation and activation of HER2. She noted that substance P increased phosphorylation of HER2 by Src, an intracellular kinase that contributes to HER2 activation. She thinks that TACR1's ability to recruit Src to HER2 could contribute to resistance to conventional HER2 inhibitors.

"Pharmacological inhibitors of HER2 inhibit kinase activity, but they don't affect activation of other kinases like Src, which binds to HER2's cytoplasmic tail via TACR1," said Almendro.

For now, Thomas thinks that the best therapeutic prospects lie in combining HER2 inhibitors with TACR1 antagonists. He said that the ideal candidate would block TACR1's ability to interact with HER2 but would not interfere with TACR1's other functions in the nervous system.

"This is an area for biased ligands," said Thomas. "There may be distinct steps that affect HER2 activation that could be selectively modulated independently of other downstream effects."

Without a side-by-side comparison in xenograft tumor models, it is not clear which—if any—existing TACR1 antagonist would be best suited to becoming a cancer therapeutic.

Merck & Co. Inc. markets the TACR1 antagonist Emend fosaprepitant dimeglumine to treat chemotherapy-induced nausea and vomiting (CINV). Three other TACR1 inhibitors are in Phase III testing for CINV, and at least five TACR1 inhibitors are in Phase I and II testing for a range of neurological and dermatological indications.

Almendro said that blocking TACR1 signaling may have the additional benefit of reducing pain and inflammation around tumors,

(Continues on p. 11)

"It's pretty definitive that knocking down *TACR1* causes loss of growth-promoting signaling by substance P. This is good evidence of a direct link between HER2 and TACR1."

—Walter Thomas,
The University of Queensland

sFGFR for achondroplasia

By Lauren Martz, Staff Writer

Achondroplasia treatments include surgical procedures to increase bone length and human growth hormone injections to stimulate growth, but neither restores normal stature. Moreover, additional interventions are required to treat the secondary consequences of short-limb dwarfism including paralysis, respiratory disorders, sleep apnea and spinal deformities.

Now, French researchers have designed a decoy version of fibroblast growth factor receptor 3 (FGFR3; CD333) that increased bone length and decreased achondroplasia-associated complications in mice compared with vehicle.¹ The molecule has a longer half-life than other clinical candidates focused on correcting abnormal signaling by FGFR3.

Achondroplasia is the most common form of short-limb dwarfism. The genetic disorder is caused by a gain-of-function point mutation in *FGFR3* that prolongs

ligand binding to the receptor and delays receptor internalization, thus increasing FGFR3 signaling.

The increased signaling ultimately inhibits normal chondrocyte function and maturation, impairing normal bone growth.

Achondroplasia research has turned toward correcting the abnormal FGFR3 signaling in children. Last year, one such treatment from **BioMarin Pharmaceutical Inc.** began clinical testing.

The company's BMN-111 is an analog of C-type natriuretic peptide (CNP; NPPC) that blocks signaling downstream of FGFR3 in the growth

plate. The molecule has completed a Phase I trial in healthy adults, and BioMarin hopes to begin a Phase II trial in patients this year or in 1Q14.

In animal models, BMN-111 was safe and restored bone growth during the growth period, resulting in bones of normal length. The compound has a half-life of 45 minutes, which VP of Pharmacological Sciences Charles O'Neill said may require daily dosing.

Now, Elvire Gouze and colleagues at **Institut National de la Santé et de la Recherche Médicale U1065** (INSERM U1065) have taken a different approach to blocking aberrant FGFR3 signaling in achondroplasia. The team designed a soluble human FGFR3 (sFGFR3) receptor that acts as a decoy for FGFR3 ligands to decrease ligand binding and receptor signaling.

Gouze is a researcher at INSERM U1065. The paper also included researchers from the **University of Paul Sabatier Toulouse III**, the **University of Nice Sophia Antipolis**, **University Hospital Center of l'Archet** and **Institute National de la Santé et de la Recherche Médicale U1043** (INSERM U1043).

In a mouse model of achondroplasia, the team subcutaneously injected 0.25 or 2.5 mg/kg of sFGFR3 twice weekly for three weeks in newborn mice.

The animals had increased skeletal growth and long-bone length and decreased mortality compared with vehicle-treated controls. Bone length in treated mice was comparable to that in healthy controls.

sFGFR3 also penetrated the cartilage matrix of the growth plate, stimulated chondrocyte maturation and increased synthesis of extracellular matrix components. These findings suggest that sFGFR3 restores chondrocyte maturation blocked by the aberrant sFGFR3 activation in achondroplasia.

The next question was whether sFGFR3 could correct achondroplasia's effects on spinal and skull abnormalities. Whereas 80% of vehicle-treated mice had spinal deformities, only 12% and 6% of mice receiving low and high sFGFR3 doses, respectively, developed abnormalities.

sFGFR3 also corrected skull length. The molecule was safe and had a half-life of about 16 hours in mice.

Data were published in *Science Translational Medicine*.

"Our treatment was effective at both restoring the stature of treated
(Continues on p. 12)

"Our treatment was effective at both restoring the stature of treated mice and preventing complications. This was critical for the treatment to have benefits over existing approaches."

— Elvire Gouze,
Institut National de la Santé et de la Recherche Médicale

(Continued from "HER2's outside help," p. 10)

and she is now conducting experiments to explore this in mouse models of breast, colon and prostate cancer, in which substance P levels are known to be elevated.

Although Almendro's current study focused on TACR1's direct effect on HER2, she nonetheless thinks that blocking substance P with antibodies will be more effective than inhibiting TACR1.

She said that there are at least two other receptors of substance P that are not likely to be affected by TACR1 inhibitors, so blocking TACR1 may not be enough, even in combination with HER2 inhibitors.

Almendro has been granted an EU patent on the use of antibodies against substance P for use in cancer. Negotiations with an undisclosed pharma to license that patent are ongoing.

Osheroich, L. *SciBX* 6(40); doi:10.1038/scibx.2013.1119
Published online Oct. 17, 2013

REFERENCES

- Garcia-Recio, S. *et al. Cancer Res.*; published online Sept. 12, 2013; doi:10.1158/0008-5472.CAN-12-4573
Contact: Vanessa Almendro, Hospital Clinic of Barcelona, Barcelona, Spain
e-mail: almendro@clinic.ub.es
- Arora, P. *et al. Oncogene* 27, 4434–4445 (2008)
- Cho, S.-G. *et al. Cancer Res.* 71, 6535–6546 (2011)
- George, A.J. *et al. Nat. Rev. Cancer* 10, 745–759 (2010)
- Mayordomo, C. *et al. J. Cell Physiol.* 227, 1358–1366 (2012)
- George, A.J. *et al. J. Cell Sci.*; published online Sept. 17, 2013; doi:10.1242/jcs.128280

COMPANIES AND INSTITUTIONS MENTIONED

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The University of Queensland, Brisbane, Queensland, Australia

mice and preventing complications. This was critical for the treatment to have benefits over existing approaches,” said Gouze.

“This strategy may also work as a treatment for very severe complications that occur due to FGFR3 mutations, such as severe achondroplasia with developmental delay and acanthosis nigricans, which is characterized by extremely short stature and intellectual disability,” said Kalina Hristova, professor of materials science and biomedical engineering at **The Johns Hopkins University**.

Halftime

Gouze said that her team needs to verify that sFGFR3’s half-life in humans is at least equivalent to that in mice.

She added, “We cannot plan a dosing regimen in humans as we need to verify the pharmacokinetic parameters in humans first. We can just say that it would certainly not be daily injections.”

O’Neill acknowledged that sFGFR3 has a longer half-life and the potential for less frequent dosing. However, he noted that “this could be a good and a bad thing. If any toxicities do arise from treatment with sFGFR3, it would take longer to resolve the toxicological response. In comparison, we have found that normal bone growth patterns are restored within one week of cessation of treatment with BMN-111.”

O’Neill also said that decoy receptors “have the potential to cause immunogenicity issues, especially when tested in higher species. Antibodies against the protein could decrease the therapeutic benefit and could also cause toxicity issues if there is any cross-reactivity for related human receptors.”

He wanted to see mice dosed with sFGFR3 for longer periods of time to characterize any immunogenicity and cross-reactivity for endogenous FGFRs.

O’Neill said that BioMarin has seen a weak immunological response to BMN-111 in animal studies, but the presence of antibodies did not affect the pharmacological activity of the drug or the safety profile. BMN-111 is 39 amino acids long, whereas sFGFR3 is about 700 amino acids long.

Hristova added that the use of a full-length protein could also be associated with high costs.

“The authors use the full-length extracellular domain of FGFR3 and produce it in mammalian cells. This treatment may be too expensive, especially if long-term therapy is required. It should be investigated if the post-translational modifications of the soluble FGFR3 are required for this application. If they are not, it may be possible to produce the protein in bacteria in a cost-effective way,” she said.

Finally, O’Neill noted the large amount of sFGFR3 needed for therapeutic activity. “The molecular characteristics of sFGFR3 don’t favor movement to the growth plate,” which is a cartilage component at the end of bones in children and adolescents that is involved in initial development and growth. “This could be the reason that high doses are required for therapeutic effect in the mice, and the researchers may need to tweak the molecule to allow easier distribution to the growth plate.”

Gouze told *SciBX* that INSERM U1065 has filed an international patent application and that the IP is available for licensing.

Martz, L. *SciBX* 6(40); doi:10.1038/scibx.2013.1120
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REFERENCES

1. Garcia, S. *et al. Sci. Transl. Med.*; published online Sept. 13, 2013; doi:10.1126/scitranslmed.3006247
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This week in therapeutics

THE DISTILLERY brings you this week's most essential scientific findings in therapeutics, distilled by *SciBX* editors from a weekly review of more than 400 papers in 41 of the highest-impact journals in the fields of biotechnology, the life sciences and chemistry. The Distillery goes beyond the abstracts to explain the commercial relevance of featured research, including licensing status and companies working in the field, where applicable.

This week in therapeutics includes important research findings on targets and compounds, grouped first by disease class and then alphabetically by indication.

| Indication | Target/marker/pathway | Summary | Licensing status | Publication and contact information |
|---------------|--|---|--|--|
| Cancer | | | | |
| Breast cancer | Neurokinin 1 substance P (TAC1; NK1); NK1 substance P receptor (TACR1); HER2 (EGFR2; ErbB2; neu) | <p>Studies in cell culture and mice suggest antagonizing NK1 or TACR1 could be useful for treating HER2⁺ breast cancer. In cultured tumor cells, NK1 increased HER2 signaling compared with vehicle. In cell culture and mouse xenografts, a small molecule TACR1 antagonist decreased HER2 signaling and tumor growth compared with saline control. Next steps include comparing the effects of TACR1 inhibitors and anti-NK1 mAbs in mouse models of breast cancer. Merck & Co. Inc. markets the TACR1 antagonist Emend fosaprepitant dimeglumine to prevent chemotherapy-induced nausea and vomiting (CINV). At least eight other TACR1 antagonists are in preclinical through Phase III testing for various neurological indications (<i>see HER2's outside help, page 10</i>).</p> <p>SciBX 6(40); doi:10.1038/scibx.2013.1121 Published online Oct. 17, 2013</p> | Patented in EU; available for licensing | Garcia-Recio, S. <i>et al. Cancer Res.</i> ; published online Sept. 12, 2013; doi:10.1158/0008-5472.CAN-12-4573 Contact: Vanessa Almendro, Hospital Clinic of Barcelona, Barcelona, Spain e-mail: almendro@clinic.ub.es |
| Breast cancer | Retinoic acid receptor responder (tazarotene induced) 1 (RARRES1; TIG1); AXL receptor tyrosine kinase (AXL; UFO) | <p><i>In vitro</i> and mouse studies suggest inhibiting TIG1 could help treat inflammatory breast cancer. Inflammatory breast cancer is a rare form of the disease characterized by cancer cells that block the lymphatic vessels in the skin covering the breast. High TIG1 expression correlated with short overall survival in patients with the disease. In cultured inflammatory breast cancer cells, small hairpin RNA against <i>TIG1</i> or an inhibitor of AXL, which is stabilized by TIG1, decreased cell proliferation, migration and invasion compared with shRNA or vehicle controls. In mice xenograft models of inflammatory breast cancer, shRNA against <i>TIG1</i> decreased tumor growth compared with shRNA control. Next steps include developing a therapeutic that inhibits TIG1 or the interaction between TIG1 and AXL. Rigel Pharmaceuticals Inc. and BerGenBio A/S have the AXL inhibitor BGB324 in Phase I testing to treat cancer. Qurient Co. Ltd. has the AXL inhibitor Q-4 in preclinical testing to treat cancer.</p> <p>SciBX 6(40); doi:10.1038/scibx.2013.1122 Published online Oct. 17, 2013</p> | Findings unpatented; available for licensing | Wang, X. <i>et al. Cancer Res.</i> ; published online Sept. 6, 2013; doi:10.1158/0008-5472.CAN-13-0967 Contact: Naoto T. Ueno, The University of Texas MD Anderson Cancer Center, Houston, Texas e-mail: nueno@mdanderson.org |
| Cancer | MHC class I polypeptide-related sequence B (MICB); killer cell lectin-like receptor subfamily K member 1 (KLRK1; CD314; NKG2D) | <p>Mouse studies suggest reducing circulating MICB levels could help treat cancer. In a mouse model of prostate cancer, expression of soluble human MICB, which is a ligand for the NK cell-activating receptor NKG2D, decreased peripheral NK cell levels and increased tumor growth and metastases compared with no MICB expression. In the model, a neutralizing antibody against MICB increased NK cell levels compared with an IgG control. Next steps include developing a humanized antibody targeting soluble MICB.</p> <p>SciBX 6(40); doi:10.1038/scibx.2013.1123 Published online Oct. 17, 2013</p> | Three patent applications filed; two available for licensing | Liu, G. <i>et al. J. Clin. Invest.</i> ; published online Sept. 9, 2013; doi:10.1172/JCI69369 Contact: Jennifer D. Wu, University of Washington, Seattle, Wash. e-mail: wuj@u.washington.edu |

This week in therapeutics (continued)

| Indication | Target/marker/pathway | Summary | Licensing status | Publication and contact information |
|------------------------------------|---|--|---|---|
| Melanoma | 3-Phosphoinositide-dependent protein kinase-1 (PDPK1); BRAF | <p>Studies in patient tumor samples and mice suggest PDPK1 inhibitors could help treat melanoma. In human primary and metastatic melanoma tumors, PDPK1 levels were higher than those in normal tissue. In mouse models of Braf-mutant melanoma, <i>Pdpk1</i> knockout increased survival and decreased primary tumor growth and lung metastases compared with normal <i>Pdpk1</i> expression. In this model, a small molecule PDPK1 inhibitor decreased tumor growth and metastasis compared with vehicle. Next steps include identifying human melanomas that might respond to PDPK1 inhibitors.</p> <p>Arno Therapeutics Inc. has AR-12 (OSU-0312), a small molecule PDPK1 inhibitor, in Phase I testing to treat lymphoma and solid tumors.</p> <p>Phusis Therapeutics Inc. has PHT-427, a small molecule inhibitor of protein kinase B (PKB; PKBA; AKT; AKT1) mRNA and PDPK1, in preclinical development to treat cancer.</p> <p>SciBX 6(40); doi:10.1038/scibx.2013.1124 Published online Oct. 17, 2013</p> | Patented by the Sanford-Burnham Medical Research Institute; licensing status undisclosed | <p>Scortegagna, M. <i>et al. Oncogene</i>; published online Sept. 16, 2013; doi:10.1038/onc.2013.383</p> <p>Contact: Zeev A. Ronai, Sanford-Burnham Medical Research Institute, La Jolla, Calif. e-mail: ronai@sbmri.org</p> |
| Cardiovascular disease | | | | |
| Ischemia/reperfusion injury | MicroRNA-27a (miR-27a); <i>VE-cadherin</i> (<i>CD144</i> ; <i>cadherin-5</i>) | <p>Mouse studies suggesting blocking the interaction between miR-27a and <i>VE-cadherin</i> transcripts could help treat ischemia. In a mouse model of hind limb ischemia, an RNA antagomir that inhibits the miR-27a-<i>VE-cadherin</i> interaction decreased edema and increased both blood flow and angiogenesis in ischemic muscle compared with a control antagomir. Next steps include evaluating the blockade of the miR-27a-<i>VE-cadherin</i> interaction in other arterial injury models and determining the therapeutic window for use of the antagomir.</p> <p>Mirrx Therapeutics A/S has an IP stake in the blockmir antagomir technology used in this work and is developing blockmirs for therapeutic and research use.</p> <p>SciBX 6(40); doi:10.1038/scibx.2013.1125 Published online Oct. 17, 2013</p> | Patent pending covering use in indications related to vascular edema; available for licensing from Bio-Link Australia Pty. Ltd. | <p>Young, J.A. <i>et al. Blood</i>; published online Sept. 5, 2013; doi:10.1182/blood-2012-12-473017</p> <p>Contact: Jennifer R. Gamble, The University of Sydney, Sydney, New South Wales, Australia e-mail: j.gamble@centenary.org.au</p> |
| Endocrine/metabolic disease | | | | |
| Diabetes | Hypoxia-inducible factor prolyl hydroxylase 3 (EGLN3; HIF-PH3; PHD3) | <p>Mouse studies suggest liver-specific inhibition of PHD3 could help treat type 2 diabetes without the toxicity of pan-PHD inhibition. In mice fed a high-fat diet, liver-specific knockout of <i>Phd3</i> improved insulin sensitivity and reversed the diabetic phenotype compared with wild-type <i>Phd3</i> expression. In the <i>Phd3</i>-deficient mice, liver-specific knockout of <i>Phd1</i> (<i>Egln2</i>; <i>Hif-ph1</i>) and <i>Phd2</i> (<i>Egln1</i>; <i>Hif-ph2</i>) did not yield additional metabolic improvements but caused hepatic steatosis. Next steps include identifying a PHD3-specific inhibitor and evaluating it in additional animal models.</p> <p>SciBX 6(40); doi:10.1038/scibx.2013.1126 Published online Oct. 17, 2013</p> | Unpatented; licensing status not applicable | <p>Taniguchi, C.M. <i>et al. Nat. Med.</i>; published online Sept. 15, 2013; doi:10.1038/nm.3294</p> <p>Contact: Amato J. Giaccia, Stanford University, Stanford, Calif. e-mail: giaccia@stanford.edu</p> |

This week in therapeutics (continued)

| Indication | Target/marker/ pathway | Summary | Licensing status | Publication and contact information |
|-------------------------------------|--|---|---|--|
| Diabetes | K(lysine) acetyltransferase 2B (KAT2B; PCAF) | <p>Mouse studies suggest antagonizing KAT2B could help lower glucose levels and help treat type 2 diabetes. In fasting mice, liver-specific RNAi knockdown of <i>Kat2b</i> prevented histone H3K9 acetylation and expression of gluconeogenic genes and decreased circulating glucose levels compared with no knockdown. In insulin-resistant mouse models of obesity and diabetes, anacardic acid, a natural product that inhibits KAT2B, decreased gluconeogenic gene expression compared with a nonspecific compound. Next steps could include developing a KAT2B antagonist.</p> <p>SciBX 6(40); doi:10.1038/scibx.2013.1127 Published online Oct. 17, 2013</p> | Patent and licensing status unavailable | <p>Ravnskjaer, K. <i>et al. J. Clin. Invest.</i>; published online Sept. 24, 2013; doi:10.1172/JCI69035</p> <p>Contact: Marc Montminy, Salk Institute for Biological Studies, La Jolla, Calif. e-mail: montminy@salk.edu</p> |
| Diabetes | Solute carrier family 30 zinc transporter member 8 (SLC30A8; ZNT8) | <p>Mouse and human studies suggest stimulating pancreatic SLC30A8 could help treat diabetes. Humans with the <i>SLC30A8</i> rs13266634 allele have an elevated risk of developing type 2 diabetes. In mice, β cell-specific knockout of <i>Slc30a8</i> impaired glucose tolerance and led to low peripheral insulin levels compared with no knockout despite elevated insulin secretion from islet cells. In the knockout mice and in humans with the rs13266634 allele, insulin clearance by the liver was greater than that seen in mice with no knockout or no risk allele. Next steps include investigating how zinc impacts insulin clearance by the liver.</p> <p>SciBX 6(40); doi:10.1038/scibx.2013.1128 Published online Oct. 17, 2013</p> | Unpatented; licensing status not applicable | <p>Tamaki, M. <i>et al. J. Clin. Invest.</i>; published online Sept. 24, 2013; doi:10.1172/JCI68807</p> <p>Contact: Yoshio Fujitani, Juntendo University Graduate School of Medicine, Tokyo, Japan e-mail: fujitani@juntendo.ac.jp</p> |
| Glycosphingolipid storage disorders | Adenosine A _{2A} receptor (ADORA _{2A}) | <p><i>In vitro</i> studies suggest ADORA_{2A} agonists could help treat Niemann-Pick disease type C1 (NPC1). ADORA_{2A} plays a role in regulating lysosomal pH and calcium ion (Ca²⁺) levels, which are downregulated in NPC1. In primary fibroblasts from patients with NPC1, the ADORA_{2A} agonist CGS21680 increased lysosomal Ca²⁺ levels and decreased cholesterol accumulation to levels comparable to those of fibroblasts from healthy controls. Next steps could include testing ADORA_{2A} agonists in animal models of NPC1. Adenosine Therapeutics LLC has the ADORA_{2A} agonist Stedivaze apadenoson in Phase III testing for use as a pharmacological stress agent in myocardial perfusion imaging (MPI). Swedish Orphan Biovitrum AB, CBT Development Ltd. and Ergomed Clinical Research Ltd. have the ADORA_{2A} agonist BVT.115959 in Phase II testing to treat pain. Forest Laboratories Inc. and Zalicus Inc. have the ADORA_{2A} agonist ALT313 in preclinical testing to treat cancer. Forest also has ALT313 in preclinical testing to treat pain. CGS21680 is a research reagent.</p> <p>SciBX 6(40); doi:10.1038/scibx.2013.1129 Published online Oct. 17, 2013</p> | Patent and licensing status unavailable | <p>Visentin, S. <i>et al. J. Neurosci.</i>; published online Sept. 25, 2013; doi:10.1523/JNEUROSCI.0558-13.2013</p> <p>Contact: Patrizia Popoli, National Institute of Health, Rome, Italy e-mail: patrizia.popoli@iss.it</p> |

This week in therapeutics (continued)

| Indication | Target/marker/pathway | Summary | Licensing status | Publication and contact information |
|-------------------------------------|---|--|--|--|
| Glycosphingolipid storage disorders | Palmitoyl-protein thioesterase 1 (PPT1) | <i>In vitro</i> and mouse studies suggest a hydroxylamine derivative could help treat infantile neuronal ceroid lipofuscinosis (INCL), a lysosomal storage disorder in which loss of PPT1 function leads to lysosomal ceroid accumulation and neuronal damage. In lymphoblasts from patients with INCL, the hydroxylamine derivative <i>N</i> -(tert-Butyl) hydroxylamine (NtBuHA) depleted lysosomal ceroids. In <i>Ppt1</i> knockout mice, NtBuHA depleted lysosomal ceroids and decreased neuronal apoptosis and increased survival compared with no treatment. Next steps include carrying out IND-enabling studies of NtBuHA. SciBX 6(40); doi:10.1038/scibx.2013.1130 Published online Oct. 17, 2013 | Patent application filed; available for licensing | Sarkar, C. <i>et al. Nat. Neurosci.</i> ; published online Sept. 22, 2013; doi:10.1038/nn.3526 Contact: Anil B. Mukherjee, National Institute of Child Health and Human Development, Bethesda, Md. e-mail: mukherja@exchange.nih.gov |
| Hepatic disease | | | | |
| Drug-induced liver injury (DILI) | Ceramide synthase 2 (CERS2) | Mouse studies suggest inhibiting CERS2 could help treat and prevent drug-induced liver injury. In mice, <i>Cers2</i> knockout protected against acetaminophen overdose-induced liver damage. The <i>Cers2</i> knockout mice also were protected from the hepatotoxic effects of D-galactosamine, carbon tetrachloride and thioacetamide, whereas wild-type mice were not. Next steps could include developing and evaluating pharmacological inhibitors of CERS2 in animal models of drug-induced liver injury. SciBX 6(40); doi:10.1038/scibx.2013.1131 Published online Oct. 17, 2013 | Patent and licensing status unavailable | Park, W.-J. <i>et al. J. Biol. Chem.</i> ; published online Sept. 9, 2013; doi:10.1074/jbc.M112.448852 Contact: Anthony H. Futerman, Weizmann Institute of Science, Rehovot, Israel e-mail: tony.futerman@weizmann.ac.il |
| Infectious disease | | | | |
| Infectious disease | Formyl peptide receptor 1 (FPR1) | Mouse studies suggest stimulating neutrophil-expressed FPR1 could help treat toxoplasmosis and other chronic gastrointestinal infections. In a mouse model of <i>Toxoplasma gondii</i> -related gastrointestinal infection, deletion of <i>Fpr1</i> decreased neutrophil recruitment and bacterial encapsulation by neutrophils and increased mortality compared with no deletion. Next steps could include exploring the therapeutic potential of <i>N</i> -formyl peptide-mediated stimulation of FPR1 in models of chronic gastrointestinal infection such as inflammatory bowel disease (IBD). SciBX 6(40); doi:10.1038/scibx.2013.1132 Published online Oct. 17, 2013 | Patent and licensing status unavailable | Molloy, M.J. <i>et al. Cell Host Microbe</i> ; published online Sept. 11, 2013; doi:10.1016/j.chom.2013.08.003 Contact: Yasmine Belkaid, National Institutes of Health, Bethesda, Md. e-mail: ybelkaid@niaid.nih.gov |
| Leishmaniasis | <i>Leishmania</i> hemoglobin receptor (HbR) | Rodent studies suggest an HbR-based vaccine could protect against visceral Leishmaniasis. <i>Leishmania</i> use HbR to acquire exogenous heme, which is required for growth. DNA sequencing of multiple strains of <i>Leishmania</i> showed that HbR is highly conserved. In mouse and hamster models of <i>Leishmania</i> infection, immunization with HbR DNA decreased splenic and hepatic parasite burden and increased T cell proliferation and survival compared with no immunization. Next steps could include testing the vaccine in primates. Mologen AG and the Infectious Disease Research Institute have a DNA-based vaccine against leishmaniasis in Phase I testing. SciBX 6(40); doi:10.1038/scibx.2013.1133 Published online Oct. 17, 2013 | Patent application filed; licensing status unavailable | Guha, R. <i>et al. Sci. Transl. Med.</i> ; published online Sept. 11, 2013; doi:10.1126/scitranslmed.3006406 Contact: Amitabha Mukhopadhyay, Indian Institute of Chemical Biology, Kolkata, India e-mail: amitabha@iicb.res.in Contact: Syamal Roy, same affiliation as above e-mail: sroy@iicb.res.in |

This week in therapeutics (continued)

| Indication | Target/marker/ pathway | Summary | Licensing status | Publication and contact information |
|--------------------------------|--|---|---|---|
| Musculoskeletal disease | | | | |
| Musculoskeletal disease | Fibroblast growth factor receptor 3 (FGFR3; CD333) | <p>Mouse studies suggest a recombinant, soluble form of FGFR3 could help treat achondroplasia, a disorder in bone growth caused by a point mutation in <i>FGFR3</i> that increases the receptor's activity. In a genetic mouse model of achondroplasia, soluble FGFR3 given twice weekly for three weeks increased bone growth and survival compared with vehicle without observable toxicity. In the mouse model, soluble FGFR3 induced chondrocyte maturation to promote bone growth and competed with endogenous mutant FGFR3. Next steps include assessing toxicity of FGFR3 in other animals.</p> <p>BioMarin Pharmaceutical Inc.'s BMN-111, a C-type natriuretic peptide (CNP; NPPC) analog that indirectly inhibits FGFR3 signaling, is in Phase I testing to treat achondroplasia (<i>see sFGFR for achondroplasia, page 11</i>).</p> <p>SciBX 6(40); doi:10.1038/scibx.2013.1134 Published online Oct. 17, 2013</p> | Patent application filed; available for licensing | <p>Garcia, S. <i>et al. Sci. Transl. Med.</i>; published online Sept. 13, 2013; doi:10.1126/scitranslmed.3006247</p> <p>Contact: Elvire Gouze, Institut National de la Santé et de la Recherche Médicale (INSERM), Nice, France e-mail: elvire.gouze@inserm.fr</p> |
| Neurology | | | | |
| Addiction | Nicotinic acetylcholine receptor $\alpha_4\beta_2$ | <p>Pharmacological and rat studies suggest the sazetidine A derivative VMY-2-95 could aid smoking cessation. Sazetidine A selectively desensitizes nicotinic acetylcholine receptor $\alpha_4\beta_2$. Chemical modification of sazetidine produced a lead compound, VMY-2-95, with receptor selectivity, affinity and desensitization efficiency similar to those for sazetidine A but with greater blood brain barrier penetration. In a rat model of nicotine addiction, subcutaneously injected VMY-2-95 decreased nicotine self-administration compared with saline control ($p < 0.05$). Next steps include scale up of VMY-2-95 synthesis to complete preclinical studies for a pre-IND package in smoking cessation.</p> <p>SciBX 6(40); doi:10.1038/scibx.2013.1135 Published online Oct. 17, 2013</p> | Patent application filed; available for licensing | <p>Yenugonda, V.M. <i>et al. J. Med. Chem.</i>; published Sept. 18, 2013; doi:10.1021/jm4008455</p> <p>Contact: Milton L. Brown, Georgetown University School of Medicine, Washington, D.C. e-mail: mb544@georgetown.edu</p> |
| Parkinson's disease (PD) | Dopamine D5 receptor | <p>Studies in rodents suggest inhibiting dopamine D5 receptor in the subthalamic nucleus (STN) could help treat PD. In brain slices from normal rats, a dopamine D5 receptor inverse agonist decreased constitutive activity of dopamine D5 receptor compared with buffer. In brain slices from normal and dopamine-depleted rats, the inverse agonist decreased burst firing in the STN compared with buffer. In motor-impaired, dopamine-depleted rats, intrasubthalamic injection of the inverse agonist increased locomotor activity and normalized cellular metabolic activity compared with saline injection. Next steps could include designing dopamine D5 receptor-specific antagonists and testing in preclinical models of PD.</p> <p>SciBX 6(40); doi:10.1038/scibx.2013.1136 Published online Oct. 17, 2013</p> | Patent and licensing status unavailable | <p>Chetrit, J. <i>et al. J. Neurosci.</i>; published online Sept. 11, 2013; doi:10.1523/JNEUROSCI.0453-13.2013</p> <p>Contact: Abdelhamid Benazzouz, University of Bordeaux Segalen, Bordeaux, France e-mail: abdelhamid.benazzouz@u-bordeaux2.fr</p> |

This week in therapeutics (continued)

| Indication | Target/marker/ pathway | Summary | Licensing status | Publication and contact information |
|---------------------------|---|--|---|---|
| Ophthalmic disease | | | | |
| Blindness | Centrosomal protein 290 kDa (CEP290) | Cell culture and biochemical studies suggest a truncated form of CEP290 could help treat Leber's congenital amaurosis (LCA) type 10. Mutations in <i>CEP290</i> have been shown to cause LCA type 10 and other diseases. Functional studies of full-length and truncated forms of CEP290 showed that absence or mutation of its microtubule-binding region disrupts normal microtubule association and causes retinal degeneration. Subsequent studies identified N- and C-terminal domains of CEP290 that were not needed for its normal activity. Planned work includes developing and testing adeno-associated viral (AAV) vector-based therapeutics containing truncated forms of CEP290 in mouse models of LCA. SciBX 6(40); doi:10.1038/scibx.2013.1137 Published online Oct. 17, 2013 | Patent application filed by the University of Pennsylvania; available for licensing | Drivas, T.G. <i>et al. J. Clin. Invest.</i> ; published online Sept. 24, 2013; doi:10.1172/JCI69448 Contact: Jean Bennett, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pa. e-mail: jebennet@mail.med.upenn.edu |
| Retinopathy | Angiopoietin 1 (ANG1; ANGPT1) | Mouse studies suggest ANG1 could help treat retinopathy of prematurity (ROP) and proliferative diabetic retinopathy (PDR). In an oxygen-induced retinopathy mouse model of ROP and PDR, intravitreal injection of Ang1 decreased avascular area, vascular leakage and retinal neuron apoptosis compared with injection of Fc control and showed greater potency than Eylea aflibercept. Next steps could include testing Ang1 in additional animal models of retinal disease. Regeneron Pharmaceuticals Inc., Bayer AG and Santen Pharmaceutical Co. Ltd. market Eylea, a human fusion protein that binds all forms of VEGF-A and placental growth factor (PGF; PlGF), to treat ocular disorders, including age-related macular degeneration (AMD), macular edema and retinal vein occlusion. SciBX 6(40); doi:10.1038/scibx.2013.1138 Published online Oct. 17, 2013 | Patent and licensing status unavailable | Lee, J. <i>et al. Sci. Transl. Med.</i> ; published online Sept. 13, 2013; doi:10.1126/scitranslmed.3006666 Contact: Gou Young Koh, Korea Advanced Institute of Science and Technology, Daejeon, South Korea e-mail: gykoh@kaist.ac.kr Contact: Ook-Joon Yoo, same affiliation as above e-mail: ojyoo@kaist.ac.kr |

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This week in techniques

THE DISTILLERY brings you this week's most essential scientific findings in techniques, distilled by *SciBX* editors from a weekly review of more than 400 papers in 41 of the highest-impact journals in the fields of biotechnology, the life sciences and chemistry. The Distillery goes beyond the abstracts to explain the commercial relevance of featured research, including licensing status and companies working in the field, where applicable.

This week in techniques includes findings about research tools, disease models and manufacturing processes that have the potential to enable or improve all stages of drug discovery and development.

| Approach | Summary | Licensing status | Publication and contact information |
|---|--|--|--|
| Assays & screens | | | |
| Virus-based <i>in vivo</i> RNAi screens to identify host interactions | <i>In vitro</i> and <i>in vivo</i> RNAi screens to identify virus-host interactions could help identify new targets to treat and prevent viral infections. The screen uses a library of Sindbis viruses that encode and deliver into host cells inhibitory artificial microRNAs that act as small interfering RNAs. In cell culture, the screen identified DEAD box polypeptide 58 (DDX58; RIG-I) and inhibitor of κ -light polypeptide gene enhancer in B cells kinase- β (IKBKB; IKK2) as key modulators of viral replication. In mice, the screen identified interferon-stimulated genes and factors involved in host transcription as modulators of viral replication. Next steps include adapting the system to study the transmission of influenza virus and the virulence of various alphaviruses. | Patent application filed covering use of RNA viruses as delivery vehicles for heterologous RNAs; available for licensing | Varble, A. <i>et al. Cell Host Microbe</i> ; published online Sept. 11, 2013; doi:10.1016/j.chom.2013.08.007 Contact: Benjamin R. tenOever, Icahn School of Medicine at Mount Sinai, New York, N.Y. e-mail: benjamin.tenoever@mssm.edu |
| Chemistry | | | |
| <i>In vitro</i> generation of branched polyketides using bacterial polyketide synthase (PKS) | A bacterial PKS capable of generating branched polyketides may aid the synthesis of complex polyketides with therapeutic potential. Existing recombinant PKSs comprise several enzymatic modules and only have the ability to generate linear polyketide structures. Chemical and structural analysis of a PKS derived from <i>Burkholderia rhizoxinica</i> showed that the enzyme uses vinylogous Michael addition to create branched polyketide backbones. Next steps include further exploring the enzymatic reactions that the newly discovered PKS can perform and using it in combination with other modular PKSs to install branches in polyketide chains. | Unpatented; unavailable for licensing | Bretschneider, T. <i>et al. Nature</i> ; published online Sept. 18, 2013; doi:10.1038/nature12588 Contact: Christian Hertweck, Leibniz Institute for Natural Product Research and Infection Biology, Jena, Germany e-mail: christian.herweck@hki-jena.de Contact: Georg Zocher, Eberhard Karls University of Tuebingen, Tuebingen, Germany e-mail: georg.zocher@uni-tuebingen.de |
| Disease models | | | |
| Photoreceptors differentiated from patient keratinocyte-derived induced pluripotent stem (iPS) cells to model ophthalmic diseases | <i>In vitro</i> and mouse studies suggest iPS cells derived from patient keratinocytes could be used to generate photoreceptor precursors to model or treat genetic retinal disorders. In iPS cells derived from keratinocytes obtained from a patient with retinal pigmentosa, differentiated iPS cells generated multilayer eyecup structures and contained a pigmented layer of cells displaying photoreceptor properties and markers. In mice, transplanted photoreceptor precursors that integrated into the eye formed mature photoreceptors. Next steps could include using the models to identify small molecules or gene replacement constructs that could help treat retinal disorders. | Patent and licensing status unavailable | Tucker, B.A. <i>et al. eLife</i> ; published online Aug. 27, 2013; doi:10.7554/eLife.00824 Contact: Edwin M. Stone, University of Iowa Carver College of Medicine, Iowa City, Iowa e-mail: edwin-stone@uiowa.edu |

This week in techniques (continued)

| Approach | Summary | Licensing status | Publication and contact information |
|--|---|--|--|
| Drug delivery | | | |
| Matrix metalloproteinase 2 (MMP2)-activated, chemotherapeutic nanocarriers for targeted drug delivery | MMP2-activated nanocarriers could provide a drug delivery vehicle for cancer chemotherapies. The nanopreparation consists of a hydrophilic, PEGylated micelle shell that is cleaved by MMP2 and releases paclitaxel bound to a cell-permeable Tat peptide. In human lung carcinoma cells, the nanopreparation had cytotoxicity comparable to that of free paclitaxel and was less toxic than paclitaxel in healthy cardiomyocytes. In mice with non-small cell lung cancer (NSCLC) xenografts, the nanopreparation showed better tumor accumulation and antitumor activity than nontargeted control micelles, conventional paclitaxel-carrying micelles and free paclitaxel. Next steps include testing the nanocarriers in additional tumor models. SciBX 6(40); doi:10.1038/scibx.2013.1142 Published online Oct. 17, 2013 | Patent status undisclosed; available for licensing | Zhu, L. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Sept. 23, 2013; doi:10.1073/pnas.1304987110 Contact: Vladimir P. Torchilin, Northeastern University, Boston, Mass. e-mail: v.torchilin@neu.edu |
| Tumor-specific delivery of chemotherapy using micelles with phenylboronic acid on their surface (PBA-micelles) | Polymeric PBA-micelles could enable tumor-specific delivery of chemotherapy. PBA has a high binding affinity for sialic acids, which are highly expressed on cancer cells but not normal cells. In a mouse melanoma cell line, PBA-micelles loaded with oxaliplatin exhibited greater uptake and cytotoxicity and longer intracellular retention times than free oxaliplatin or oxaliplatin-loaded micelles lacking PBA. In a mouse model of melanoma, oxaliplatin-loaded PBA-micelles had greater accumulation in primary tumors and lung metastases and decreased tumor growth compared with free oxaliplatin or oxaliplatin-loaded micelles lacking PBA. Future studies could include generating and testing PBA-micelles loaded with other chemotherapeutics. SciBX 6(40); doi:10.1038/scibx.2013.1143 Published online Oct. 17, 2013 | Patent and licensing status unavailable | Deshayes, S. <i>et al. J. Am. Chem. Soc.</i> ; published online Sept. 12, 2013; doi:10.1021/ja406406h Contact: Kazunori Kataoka, The University of Tokyo, Tokyo, Japan e-mail: kataoka@bmw.t.u-tokyo.ac.jp |
| Drug platforms | | | |
| Inhibition of methyl-CpG binding domain protein 3 (MBD3) for deterministic and synchronized reprogramming to pluripotency | <i>In vitro</i> studies suggest depletion of Mbd3 can improve the efficiency of reprogramming somatic cells to a pluripotent state over short time periods. Expression of <i>Oct4</i> , <i>Sox2</i> , <i>Klf4</i> and <i>c-Myc</i> (<i>Myc</i>) reprograms somatic cells into induced pluripotent stem (iPS) cells. In murine epiblast stem cells, small interfering RNA against Mbd3 improved the reprogramming efficiency of the 4 transcription factors to 80% at 5 days, whereas control siRNA caused a 10% improvement. In <i>Mbd3</i> -depleted mouse embryonic fibroblasts and human fibroblasts, expression of the transcription factors resulted in about 100% reprogramming efficiency by day 8, whereas wild-type cells had only 20% efficiency. Next steps could include incorporating MBD3 depletion into reprogramming protocols that companies use to generate isogenic and disease-relevant iPS cell lines. SciBX 6(40); doi:10.1038/scibx.2013.1144 Published online Oct. 17, 2013 | Patent pending; available for nonexclusive licensing | Rais, Y. <i>et al. Nature</i> ; published online Sept. 18, 2013; doi:10.1038/nature12587 Contact: Jacob H. Hanna, Weizmann Institute of Science, Rehovot, Israel e-mail: jacob.hanna@weizmann.ac.il |
| Stabilizing, camelid-derived nanobodies to facilitate generation of crystal structures of GPCRs bound to low-affinity, natural ligands | Stabilizing, camelid-derived antibody fragments called nanobodies could be useful for generating the crystal structure of GPCRs bound to low-affinity, natural ligands. A camelid nanobody with high affinity for the activated form of adrenergic receptor β_2 (ADRB2) was used to stabilize the receptor. This enabled the crystallization and resolution of the receptor's structure in complex with three chemically distinct ligands, including the low-affinity ligand adrenaline. The receptor conformation was similar for all ligands. Next steps could include applying the approach to other therapeutically relevant GPCR and low-affinity ligand pairs. Ablynx N.V., who was not involved in the current study, has multiple nanobodies in clinical and preclinical development for various diseases. SciBX 6(40); doi:10.1038/scibx.2013.1145 Published online Oct. 17, 2013 | Patent and licensing status unavailable | Ring, A.M. <i>et al. Nature</i> ; published online Sept. 22, 2013; doi:10.1038/nature12572 Contact: Brian K. Kobilka, Stanford University, Stanford, Calif. e-mail: kobilka@stanford.edu Contact: Christopher Garcia, same affiliation as above e-mail: kcgarcia@stanford.edu |

This week in techniques (continued)

| Approach | Summary | Licensing status | Publication and contact information |
|---|--|--|---|
| Synthesis of therapeutic peptides resistant to degradation by serine proteases | A method to render therapeutic peptides resistant to serine proteases could increase their <i>in vivo</i> stability. The method involves replacing the amino acid adjacent to a serine protease cleavage site with an analog containing a substituted β -carbon during peptide synthesis. Modified versions of glucagon-like peptide-1 (GLP-1), neuropeptide Y (NPY) and other therapeutic peptides incubated with dipeptidyl peptidase-4 (DPP-4; CD26), DPP-8 or other serine proteases had <i>in vitro</i> half-lives at least 10-fold greater than those of the corresponding unmodified peptides. Ongoing work includes testing the modified GLP-1 peptide in animal models of diabetes and metabolic syndrome. Arisaph Pharmaceuticals Inc. has stabilized GLP-1s in preclinical development to treat diabetes. | Patented by the Tufts University School of Medicine; licensed to Arisaph Pharmaceuticals | Heard, K.R. <i>et al. J. Med. Chem.</i> ; published online Sept. 17, 2013; doi:10.1021/jm400423p Contact: William W. Bachovchin, Tufts University Sackler School of Graduate Biomedical Sciences, Boston, Mass. e-mail: william.bachovchin@tufts.edu |
| Imaging | | | |
| Microtubule-associated protein- τ (MAPT; TAU; FTDP-17)-staining PET reagent for imaging Alzheimer's disease (AD) pathology | Mouse and human studies suggest PET compounds could be useful for imaging TAU neurofibrillary tangles in AD and other tauopathies. In brain tissue samples from patients with AD and a mouse model of TAU neurofibrillary tangle formation, <i>in vitro</i> delivery of fluorescently labeled phenyl, pyridinyl-butadienyl-benzothiazole or benzothiazolium compounds led to detection of TAU-containing neurofibrillary tangles. In the same mice and in patients with AD, PET imaging with radiolabeled versions of the compounds detected TAU accumulation in the neocortical and limbic regions of the brain. Next steps include correlating the distribution and degree of PET staining with postmortem TAU histopathology and evaluating the agents in patients who have mild cognitive impairment. | Patent pending; available for licensing | Maruyama, M. <i>et al. Neuron</i> ; published online Sept. 18, 2013; doi:10.1016/j.neuron.2013.07.037 Contact: Makoto Higuchi, National Institute of Radiological Sciences, Chiba, Japan e-mail: mhiguchi@nirs.go.jp |
| Markers | | | |
| 2-Amino adipic acid as a predictive marker for type 2 diabetes | A study in humans suggests measuring concentrations of 2-amino adipic acid in blood could help predict the risk of developing type 2 diabetes. A retrospective analysis of 70 metabolites measured in the blood of 350 patients with type 2 diabetes and 350 controls at risk of developing the disease showed that elevated 2-amino adipic acid levels correlated with a diagnosis of type 2 diabetes 12 years later ($p < 0.0001$). Next steps include prospective studies examining the relationship between 2-amino adipic acid, disease progression and response to type 2 diabetes therapies. | Patent pending; available for licensing | Wang, T.J. <i>et al. J. Clin. Invest.</i> ; published online Sept. 16, 2013; doi:10.1172/JCI64801 Contact: Robert E. Gerszten, Massachusetts General Hospital, Charlestown, Mass. e-mail: rgerszten@partners.org Contact: Thomas J. Wang, Vanderbilt University Medical Center, Nashville, Tenn. e-mail: thomas.j.wang@vanderbilt.edu |
| Kaposi sarcoma-associated herpes virus (KSHV; HHV-8) as a biomarker for castration-resistant prostate cancer (CRPC) | Cell-based studies suggest KSHV infection might serve as a marker for CRPC. In androgen-insensitive prostate cancer cell lines, KSHV infection increased proliferation and anchorage-independent cell growth compared with no infection. In androgen-sensitive prostate cancer cells, KSHV infection increased androgen-independent growth and epithelial-to-mesenchymal transition (EMT) compared with no infection. Next steps include exploring mechanisms of KSHV-induced EMT as markers of disease metastasis and treatment resistance. | Patent and licensing status undisclosed | Mygatt, J.G. <i>et al. Cancer Res.</i> ; published online Sept. 4, 2013; doi:10.1158/0008-5472.CAN-12-4196 Contact: Johnan A.R. Kaleeba, Uniformed Services University of the Health Sciences, Bethesda, Md. e-mail: johnan.kaleeba@usuhs.edu |

This week in techniques (continued)

| Approach | Summary | Licensing status | Publication and contact information |
|---|---|---|---|
| Three-gene signature predictive of indolent prostate cancer | A three-gene signature could help identify patients who have less aggressive forms of prostate cancer. Gene expression analyses of aging and senescence genes and subsequent analysis of samples from patients who have indolent prostate cancer led to the development of a signature consisting of <i>fibroblast growth factor receptor 1 (FGFR1; CD331)</i> , <i>cyclin-dependent kinase inhibitor 1A (p21, Cip1; CDKN1A; CIP1)</i> and <i>peripheral myelin protein 22 (PMP22)</i> . In a retrospective analysis of patient biopsy samples, expression of proteins in the signature was higher in patients who did not have disease progression. Next steps include prospective and retrospective trials to evaluate this biomarker panel on biopsy samples from independent cohorts. SciBX 6(40); doi:10.1038/scibx.2013.1150 Published online Oct. 17, 2013 | Patent application filed; available for licensing | Irshad, S. <i>et al. Sci. Transl. Med.</i> ; published online Sept. 11, 2013; doi:10.1126/scitranslmed.3006408 Contact: Cory Abate-Shen, Columbia University Medical Center, New York, N.Y. e-mail: cabateshen@columbia.edu Contact: Andrea Califano, same affiliation as above e-mail: califano@c2b2.columbia.edu |



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